Nos. 2022-2217, 2023-1021

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

UNITED THERAPEUTICS CORPORATION,

Plaintiff-Cross-Appellant,

v.

LIQUIDIA TECHNOLOGIES, INC.,

Defendant-Appellant.

On Appeal from a Judgment of the United States District Court for the District of Delaware, No. 20-cv-755 (Andrews, J.)

CROSS-APPELLANT'S PETITION FOR PANEL REHEARING AND REHEARING EN BANC

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CERTIFICATE OF INTEREST

Counsel for Cross-Appellant certifies the following:

1. The full name of every party represented by me is:

United Therapeutics Corporation.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

None.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party represented by me are:

BlackRock Inc. may own 10% or more of the stock of United Therapeutics Corporation.

4. The names of all law firms and the partners or associates that appeared for the party now represented by me in the trial court or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

MORRIS, NICHOLS, ARSHT & TUNNELL LLP: Jack B. Blumenfeld; Michael J. Flynn; Sarah Elizabeth Simonetti

MCDERMOTT, WILL & EMERY LLP: Ian B. Brooks; Timothy M. Dunker; Mandy H. Kim; Amy Mahan; Katherine Pappas; Joshua Revilla; Jiaxiao Zhang

WILSON, SONSINI, GOODRICH & ROSATI: Joshua Mack

GOODWIN PROCTER LLP: Joel Broussard; Harrison Gunn; Eric Levi; Huiya Wu

BOIES SCHILLER FLEXNER LLP: Bill Ward

5. The title and number of any case known to me to be pending in this or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal are:

None.

6. Any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees):

None.

August 23, 2023 /s/ *Jaime A. Santos*
Jaime A. Santos

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GLOSSARY

'066 Patent	U.S. Patent No. 9,593,066
'793 Patent	U.S. Patent No. 10,716,793
ANDA	Abbreviated New Drug Application
DMF	drug master file
FDA	United States Food and Drug Administration
Liquidia	Defendant-Appellant Liquidia Technologies, Inc.
Moriarty 2004	Moriarty et al., *The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15*, 69 J. Org. Chem. 1890-1902 (2004) (Appx29406-29418)
NDA	New Drug Application
PTO	United States Patent and Trademark Office
UTC	Plaintiff-Cross-Appellant United Therapeutics Corporation

RULE 35(b) STATEMENT

Based on my professional judgment, I believe the panel decision is contrary to the following precedents:

1. *Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271 (Fed. Cir. 2013)

2. *Amgen Inc. v. F. Hoffman–La Roche Ltd.*, 580 F.3d 1340 (Fed. Cir. 2009)

RULE 40(a)(2) STATEMENT

The panel overlooked the following points of law:

1. Because the infringement analysis in the Hatch-Waxman context focuses on the four corners of an applicant's New Drug Application, the fact that the applicant has not yet infringed—or merely pledges not to infringe—is insufficient to avoid liability. *See Sunovion*, 731 F.3d at 1278-1280.

2. "[S]tructural and functional differences" imparted by the process in a product-by-process claim are relevant to novelty, regardless of whether those differences are explicitly recited in the claim, and the party asserting anticipation bears the burden of proving all features of the claimed product are the same as those disclosed in the prior art. *Amgen,* 580 F.3d at 1369-1370.

August 23, 2023 /s/ *Jaime A. Santos*
Jaime A. Santos

INTRODUCTION

United Therapeutics Corporation ("UTC") has pioneered several inventions related to the treatment of pulmonary hypertension using treprostinil. In the proceedings below, the district court found one of UTC's patents valid and infringed but held certain claims of UTC's '066 Patent not infringed and the remaining claims invalid. The '066 Patent concerns a novel process for making treprostinil and the resulting improved pharmaceutical composition.

The panel's decision upholds two errors of law that, without correction, will create substantial confusion for life sciences companies and the patent community. First, the panel erred in holding that Liquidia would not infringe Claims 6 and 8 of the '066 Patent. Those claims cover storage of treprostinil salt at ambient temperature. The New Drug Application (NDA) for Liquidia's proposed treprostinil product allows storage at ambient temperature. Relying on "Liquidia's representations to the FDA that it would store treprostinil sodium between 2°C and 8°C," the panel held that "[w]ithout a showing that Liquidia stores treprostinil at ambient temperature, there can be no infringement of the claims." Op. 22-23. That holding runs afoul of this Court's decision in *Sunovion*

Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc., 731 F.3d 1271 (Fed. Cir. 2013). As *Sunovion* makes clear, in a Hatch-Waxman case the question is not whether the applicant *has already* infringed—or whether it *promises* that it will not infringe in the future—but whether its NDA seeks permission to do so. *Id.* at 1278-1280. Here, the NDA permits infringement, and Liquidia has never amended its NDA to foreclose such infringement.

Second, the panel erred in holding that the remaining claims of the '066 Patent are invalid. Claim 1-3, 6, and 9 of the '066 Patent are product-by-process claims: they claim a composition defined by the claimed process, which results in a unique product with reduced levels of certain difficult-to-remove-impurities. The panel determined that the relevant claims are anticipated over a prior art publication, Moriarty 2004, that described an undisputedly *different* process for manufacturing treprostinil and disclosed no information concerning the specific impurities addressed in the '066 Patent claims. The panel reasoned that because the claims at issue are "product claims," "they are anticipated by a disclosure of the same product *irrespective of the processes by which they are*

made"—without analyzing any product differences imparted by the processes in the claims. Op. 21 (emphasis added). But that analysis conflicts with this Court's decision in *Amgen Inc. v. F. Hoffman–La Roche Ltd.*, 580 F.3d 1340 (Fed. Cir. 2009). There, the Court held that "structural and functional differences" imparted by the process in a product-by-process claim are relevant to novelty, and a patent challenger asserting anticipation bears the burden of proving that those features of the claimed product, whether or not expressly recited in the claim, are disclosed in the prior art. *Id.* at 1366-1370. Here, the panel disregarded the reduction of specific impurities recited in the claims and relied on the total purity described in the prior art, which says nothing about the impurities to which the claims are directed.

Each error warrants rehearing—either by the panel or the full Court. If left to stand, the panel's misapplication of *Sunovion* will encourage manipulation of the carefully calibrated Hatch-Waxman framework. Under the panel's decision, an applicant can file a product application that on its face seeks approval to infringe but avoid a judgment of infringement through the simple expedient of promising that it will elect

to take superfluous steps to avoid infringing in the future. Hatch-Waxman trials will drift from focusing on the four corners of the FDA application to credibility contests and prognostication about what will or will not happen in the future.

The panel's misapplication of *Amgen* will have equally deleterious consequences. Product-by-process claims are an important vehicle for inventors to protect novel and innovative products that are "difficult or impossible" to fully analyze and describe except in reference to its manufacturing process. *Abbott Labs. v. Sandoz Inc.*, 566 F.3d 1282, 1294 (Fed. Cir. 2009) (en banc). The panel's disregard of those differences under an erroneous standard will stifle future innovation and spell confusion and uncertainty for existing patentees.

BACKGROUND

I. The '066 Patent

The '066 Patent claims are directed to a process for preparing a pharmaceutical composition of treprostinil that comprises alkylation, hydrolysis, and salt formation and isolation steps, and the improved product of that process. Op. 7-8. Claims 1-3, 6 and 9 are product-by-process claims, while claim 8 is a process claim. The claims specify that the salt

formation and isolation reduce a specific set of hard-to-remove impurities: the impurities generated during alkylation and hydrolysis. *Id.* Claims 6 and 8 require storage of the salt at ambient temperature. *Id.* The district court construed "ambient temperature" to mean "room temperature (equal to or less than the range of 15°C to 30°C)." Appx00031.

The PTO issued the '066 Patent over a prior art reference, Moriarty 2004, that described a different process for manufacturing treprostinil, based on differences in the resulting impurities profile. Appx03825; Appx29406-29418. The text of Moriarty 2004 reports an overall purity of the final product but is undisputedly silent on the presence of any specific impurities, including those identified in the claims. Liquidia never argued that any impurity profile was inherently disclosed in Moriarty 2004. Appx31039[1] The PTAB denied institution of inter partes review of the '066 Patent claims over Moriarty 2004 and other prior art based on differences in the impurities profile. Appx32004.

[1] While Liquidia presented evidence at trial concerning UTC's commercial treprostinil manufacturing process, Liquidia expressly waived any argument that the results of the commercial process were evidence of disclosures inherent in Moriarty 2004. Appx31039. Liquidia also disclaimed the on-sale bar as a ground for invalidity, rendering any evidence of UTC's confidential commercial process irrelevant to anticipation. *Id.*

II. Liquidia's Treprostinil Product and NDA

Liquidia's NDA seeks approval to market a product using treprostinil sodium manufactured by another company, Yonsung, which stores the isolated treprostinil salt without any requirement to store it in refrigerated (*i.e.* non-ambient) conditions. Liquidia's NDA specifically incorporates Yonsung's drug master file (DMF), including all properties and characteristics of the treprostinil sodium as described in the DMF, and it represents to FDA that the treprostinil sodium is stable at room temperature for six months, enclosing stability data to that effect. *See* Appx13596 (incorporating DMF's information about treprostinil sodium's "physical and chemical properties, characterization, … and stability attributes"); Appx13802, Appx14209, Appx14211, Appx14219 (NDA incorporating DMF's stability information); Appx14207 (NDA "allowing review" of DMF); Appx14739-14772 (DMF explaining ambient-temperature stability); *see* Appx13039(59:4-14); Appx13123(393:17-19). The NDA also offers clinical-trial data based on batches of Liquidia's bulk powder prepared from Yonsung's isolated treprostinil salt that was stored at ambient temperature and characterizes these batches (as it must for approval) as "representative" of the product Liquidia plans to

market. *See, e.g.*, Appx13049(98:14-99:15); Appx13677; Appx14212; Appx14888-14889; Appx14920-14921. To be sure, Yonsung's DMF recommends that the treprostinil salt be stored below ambient temperature, but it does not *require* as much for purposes of stability or safety. Nor does FDA. The DMF says only that the treprostinil salt "*[s]hould* be kept in a tight container, … and stored at 2°C to 8°C"—a permissive provision,[2] as Liquidia's own expert agreed. Appx13124(396:18-24).

Moreover, the record showed that Yonsung and Liquidia routinely disregarded the DMF's storage suggestion. Undisputed evidence showed that Yonsung frequently stored treprostinil salt well below 2°C for lengthy periods (days and weeks). *See* Appx13108(332:24-333:15); Appx13109(336:16-338:15); Appx14921. Yet Liquidia accepted those shipments and used that treprostinil salt to prepare its product. *See* Appx13108(332:24-333:15); Appx13109(336:16-338:15); Appx14921. Treprostinil salt was also stored above 8°C, and again Liquidia accepted those shipments just as it did with batches that stayed within the 2°-8°

[2] *See, e.g.*, *United States v. UPS Customhouse Brokerage, Inc.*, 575 F.3d 1376, 1382 (Fed. Cir. 2009).

range. Appx14921 (treprostinil sodium experiencing ambient temperature); Appx14193 (explaining that LGM released treprostinil sodium shipment stored at ambient temperature for nine days), Appx14175 (Liquidia accepting delivery); Appx13582 (logging temperatures below -20°C and above 16°C). Only *after* Liquidia was sued and its witness responsible for analytical testing was deposed about those batches did Liquidia assert that they would not be used to make a pharmaceutical product that would be marketed for sale, despite every indication to the contrary until then. Appx13112(348:15-350:2).

Additionally, the record showed many shipments, including batches the NDA describes as "representative," where the storage temperature was not monitored at all. *See* Appx14932-14948 (lacking temperature data); Appx14949-14962 (same); Appx14995-15020 (same). Here too, Liquidia did not refuse shipment. *See* Appx14932-14948; Appx14949-14962; Appx14995-15020. Refrigerated storage is not—and has never been—a requirement for Liquidia. It certainly is not a condition of FDA approval.

III. The Panel's Decision

As relevant to this Petition, the panel affirmed the district court's conclusion that Liquidia did not infringe claims 6, 8, and 9 of the '066 Patent, reasoning that UTC had not proved actual past infringement beyond the NDA: "Without a showing that Liquidia stores treprostinil at ambient temperature, there can be no infringement of the claims." Op. 22-23. The panel also affirmed the district court's conclusion that claims 1-3, 6, and 9 of the '066 Patent are invalid as anticipated, holding that the product-by-process claims were anticipated "irrespective of the process by which they are made," and pointing to a purported absence of evidence *from UTC* proving "*differences* between the Moriarty treprostinil and the claimed treprostinil." Op. 21.

ARGUMENT

I. The panel's decision on infringement of the storage claims is contrary to this Court's decision in *Sunovion*.

The "Hatch-Waxman framework presents a different set of circumstances than those which underlie an ordinary infringement action." *Caraco Pharm. Labs., Ltd. v. Forest Labs., Inc.*, 527 F.3d 1278, 1291 (Fed. Cir. 2008). Filing a §505(b)(2) NDA is an artificial act of infringement, 35 U.S.C. §271(e)(2), so the focus is on the NDA: what an "applicant asks

for and receives approval to market, if within the scope of a valid claim, is an infringement." *Sunovion*, 731 F.3d at 1279.

Two important principles emerge from this background. First, plaintiffs are not required to prove actual past infringement to win a *pre*-launch infringement judgment in a Hatch-Waxman suit. Instead, the factfinder asks only whether the proposed product that the applicant "is asking the FDA to approve for sale falls within the scope of an issued patent." *Id.* at 1278. If the answer is yes, then "a judgment of infringement must necessarily ensue." *Id.* Second, a finding of infringement cannot be "overrid[den]" by the applicant's "pledging not to infringe." *Id.* at 1280. Once the applicant has sought FDA approval to sell a product that falls within the scope of an issued patent, "[s]imply saying 'But I won't do it' is not enough to avoid infringement." *Id.* at 1278, 1280. Why? As this Court explained, "it would be practically impossible" to monitor the applicant's compliance with its "pledge" to not avail itself of what the NDA permits once FDA approval is granted. *Id.* at 1279.

The panel's decision disregarded these principles. Relying on "Liquidia's representations to FDA that it would store treprostinil sodium between 2°C and 8°C," the panel held that "[w]ithout a showing

that Liquidia stores treprostinil at ambient temperature, there can be no infringement of the claims." Op. 22-23. But as *Sunovion* makes clear, just the opposite is true. The question is not whether Liquidia *has already* infringed—or whether it *promises* not to infringe in the future—but whether its NDA "is asking the FDA to approve for sale [a product that] falls within the scope of an issued patent." *Sunovion*, 731 F.3d at 1278.

Liquidia's NDA is clear: the NDA allows Liquidia to store treprostinil sodium at ambient temperature. While the district court recited a finding that the NDA requires treprostinil sodium to be stored between 2°C and 8°C, Appx00025, that conclusion was premised on language that is plainly permissive, *see* Appx14736 ("STORAGE: *Should* be kept in a tight container, protected from moisture and light and stored at 2°C to 8°C." (emphasis added)); *see also supra*, pp. 7. Indeed, the district court elsewhere effectively acknowledged this, noting "the fact that Liquidia might, in some circumstances, be permitted to use TN exposed to ambient temperatures" under the NDA. Appx00032. And if there were any doubt that Liquidia is not required to store the treprostinil salt at 2°C to 8°C, its own conduct resolves it. Liquidia touted the stability of treprostinil

at ambient temperature. *See supra*, p. 6. It incorporated a specification that imposes no storage-temperature requirement. *See supra*, pp. 5-6. And it relied on treprostinil manufactured at ambient temperatures in representative batches offered for FDA approval. *See supra*, p. 8.[3] Thus, because Liquidia's NDA allows for ambient-temperature storage, it is seeking approval to sell an infringing product under *Sunovion*. There is no way to square the panel's contrary conclusion with that precedent.

If left to stand, the panel's decision will upset the carefully calibrated Hatch-Waxman regime. The Hatch-Waxman Act strikes a "compromise between two competing sets of interests: those of innovative drug manufacturers, who had seen their effective patent terms shortened by the testing and regulatory processes; and those of generic drug manufacturers, whose entry into the market upon expiration of the innovator's patents had been delayed by similar regulatory requirements." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1358 (Fed. Cir. 2003). One

[3] While at trial, Liquidia pointed to its own internal operating procedures as purported controlling storage conditions, but its corporate witnesses admitted that it can change those procedures without even notifying FDA. Appx13080(224:14-17); Appx13082(231:19-25).

aspect of that compromise is channeling disputes about patent protections into pre-launch litigation, by making the filing of a §505(b)(2) NDA an artificial act of infringement. Given the timing and nature of such suits, the inquiry naturally focuses on the four corners of the applicant's NDA: as the Court explained in *Sunovion*, "it would be practically impossible" to monitor the applicant's compliance with its "pledge" to not avail itself of what the NDA permits once FDA approval is granted. 731 F.3d at 1279.

The panel's decision upends that delicate balance. Now, an applicant can file an NDA or ANDA that permits infringing conduct *on its face*. All the applicant has to do is point to a lack of past infringement (which an applicant can always do in the Hatch-Waxman pre-approval regime) and promise not to infringe in the future. That promise is unenforceable—and that is the point. The panel's decision charts a course for applicants wishing to skirt valid patent protections.

II. The panel's decision on anticipation of the product-by-process claims is contrary to this Court's decision in *Amgen*.

The panel's decision interjects substantial confusion into the anticipation inquiry for the entire class of product-by-process claims. This Court made unequivocally clear in *Amgen* that product-by-process claims

are entitled to the same presumption of validity that, by statute, applies to all patent claims and can only be overcome by clear and convincing evidence. 580 F.3d at 1366-1367; 35 U.S.C. §282. While the novelty of product-by-process claims rests on differences between the claimed product and the prior art, the Court has made equally clear that "structural and functional differences" imparted by the process used to make that product are relevant to anticipation, regardless of whether those differences are explicitly recited in the claim. *Amgen,* 580 F.3d at 1369-1370; *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012). Thus, when a party challenges the validity of a product-by-process claim over a prior art reference disclosing a different prior-art process, it is the patent challenger, not the patentee, that bears the burden of proving that the product claimed in the product-by-process claim is the same in all relevant respects to the product made by the prior-art process. *Amgen*, 580 F.3d at 1367.

Here, the relevant aspect of the claimed product is the level of specific impurities at the end of the process. The claims are directed to a "pharmaceutical composition" of treprostinil that results from a specific process of alkylation, hydrolysis, and salt formation and isolation, during

which specific impurities that were generated during alkylation and hydrolysis are reduced during salt formation and isolation. These impurities are especially difficult to remove because of their similarities in structure to the active compound: treprostinil. The plain language of the claims requires that the resulting product, *i.e.* the "pharmaceutical composition," has lower "impurities resulting from prior alkylation and hydrolysis steps" after the claimed salt formation and isolation steps. Thus, under this Court's precedent, to find the claims anticipated, the prior art must be shown to be a "pharmaceutical composition," with the same reduced levels of "impurities resulting from prior alkylation and hydrolysis" as the claimed product. This legally relevant comparison *never* occurred.

Instead, the district court found the claims anticipated over a prior art publication, Moriarty 2004, that described a different process for manufacturing treprostinil—one that includes alkylation and hydrolysis to synthesize treprostinil but does not include salt formation and isolation steps that reduce the specific impurities generated during alkylation and hydrolysis. Appx29418; Appx00045. It also provided no express disclosure about the specific impurities profile present in the resulting

treprostinil product, and Liquidia waived any inherency argument. Appx31039. But the court did not hold Liquidia to its burden of establishing that the prior art disclosed the claimed *composition* with the impurities profile resulting from the claimed process—*i.e.* lower "impurities resulting from prior alkylation and hydrolysis steps." Instead, it based its holding on findings that Moriarty 2004 disclosed the claimed treprostinil *compound* with the *overall* purity level (99.7%) described in the patent specification—which says nothing about the levels of specific alkylation and hydrolysis impurities imparted by the claimed salt formation process—and placed the burden on UTC to prove any differences in the levels of specific impurities. And there is a reason that Liquidia chose to use the process recited in the '066 Patent claims rather than one of several prior-art processes, such as the process disclosed by Moriarty 2004: the resulting product is improved.

In affirming, the panel repeated the district court's errors—(1) ignoring structural and functional differences in impurities imparted by the manufacturing process, and (2) wrongly placing the burden on UTC to prove *differences* between the prior art and the claimed products' impurities rather than on Liquidia to prove they are the *same*. As evident

from the panel's analysis, it ignored the critical inquiry into structural and functional differences imparted by the manufacturing process, as required under *Amgen*. The panel reasoned that because the claims at issue are "product claims," "they are anticipated by a disclosure of the same product *irrespective of the processes by which they are made*." Op. 21 (emphasis added). This of course assumes the conclusion (*i.e.*, that the impurities of the products are the "same"), without holding Liquidia to its burden of proving that the process made no difference.

By ignoring altogether the differences imparted by the process in the claims, the panel limited its assessment to the total purity level of the treprostinil compound and the presence of any undifferentiated impurities: "[T]he district court did not clearly err in finding that these claims are anticipated by the Moriarty reference, which discloses treprostinil with impurities." Op. 21 (going on to compare the *total purity* of treprostinil disclosed in the Moriarty 2004 publication with the non-limiting patent specification). The panel overlooked entirely the absence of any record evidence that Moriarty 2004 disclosed the specific impurities levels in the treprostinil product it described or that those levels were the same as those of the claimed product. Instead, in direct contradiction to

Amgen, the panel placed the burden on UTC to prove differences between the prior art and claimed products: "United Therapeutics did not provide any expert or fact witness … providing testimony identifying any structural or functional differences between the Moriarty treprostinil and the claimed treprostinil." Op. 21. This turns the statutory presumption of validity on its head.[4]

Unless corrected, the panel's anticipation analysis will create substantial confusion on the standard for patentability of product-by-process claims. Product-by-process claims are an important vehicle for inventors to protect novel and innovative products that are "difficult or impossible" to fully analyze and describe except in reference to its manufacturing process. *Abbott Labs. v. Sandoz Inc.*, 566 F.3d 1282, 1294 (Fed. Cir. 2009) (en banc). When inventors create a new process that generates a new and improved product, they are entitled to protection of that product based on the features imparted by the process without having to explic-

[4] Compounding the misapplication of the statutory burden, the district court found in its infringement analysis that the patented process *in fact* reduced the claimed alkylation and hydrolysis impurities—yet ignored this evidence of novelty when evaluating validity. Appx00025; Appx13068-13070(176:5-180:17, 183:22-184:21).

itly recite those features in detail. Here, the PTO recognized the structural and functional differences imparted by salt formation and isolation process in granting the claims at issue, and rejecting post-grant challenges to them. Appx03825; Appx32004. The district court and panel's cursory dismissal of those differences under an erroneous standard creates substantial confusion in the proper standard by which the validity of product-by-process claims are assessed.

CONCLUSION

The Court should grant panel rehearing or rehearing en banc.

August 23, 2023

Respectfully submitted.

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ADDENDUM

United States Court of Appeals for the Federal Circuit

UNITED THERAPEUTICS CORPORATION,
Plaintiff-Cross-Appellant

v.

LIQUIDIA TECHNOLOGIES, INC.,
Defendant-Appellant

2022-2217, 2023-1021

Appeals from the United States District Court for the District of Delaware in No. 1:20-cv-00755-RGA-JLH, Judge Richard G. Andrews.

Decided: July 24, 2023

SANYA SUKDUANG, Cooley LLP, Washington, DC, argued for defendant-appellant. Also represented by JONATHAN DAVIES; DEEPA KANNAPPAN, Palo Alto, CA; ERIK BENTON MILCH, Reston, VA.

WILLIAM M. JAY, Goodwin Procter LLP, Washington, DC, argued for plaintiff-cross-appellant. Also represented by WILLIAM COVINGTON JACKSON, JAIME SANTOS, ROHINIYURIE TASHIMA, JENNY J. ZHANG; GERARD JUSTIN CEDRONE, Boston, MA; ADAM WILLIAM BURROWBRIDGE. McDermott Will & Emery, LLP, Washington, DC; DOUGLAS H. CARSTEN, ARTHUR PAUL DYKHUIS, Irvine, CA;

SHAUN R. SNADER, United Therapeutics Corporation, Washington, DC.

Before LOURIE, DYK, and STOLL, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Liquidia Technologies, Inc. ("Liquidia") appeals from a decision of the United States District Court for the District of Delaware holding that (1) claims 1, 4, and 6–8 of U.S. Patent 10,716,793 ("the '793 patent") are not invalid and are infringed by Liquidia and (2) claims 1–3 of U.S. Patent 9,593,066 ("the '066 patent") are invalid as anticipated, but are otherwise infringed by Liquidia. United Therapeutics Corporation ("United Therapeutics") cross-appeals from the court's decision holding that (1) claims 1–3, 6, and 9 of the '066 patent are invalid as anticipated and (2) claims 6, 8, and 9 of the '066 patent are not infringed by Liquidia. *See United Therapeutics Corp. v. Liquidia Techs., Inc.*, 624 F. Supp. 3d 436 (D. Del. 2022) ("*Decision*"). For the reasons provided below, we affirm.

BACKGROUND

United Therapeutics holds New Drug Application ("NDA") No. 022387 for Tyvaso®, an inhaled solution formulation of treprostinil approved for the treatment of pulmonary hypertension ("PH"). Pulmonary hypertension is a potentially life-threatening condition characterized generally by abnormally high blood pressure in the lungs. For many patients, treprostinil is used in treating pulmonary hypertension because it is a vasodilator that reduces vasoconstriction in the pulmonary vasculature, thereby decreasing blood pressure.

Experts consider that there are five subgroups of pulmonary hypertension: Group 1, pulmonary arterial hypertension ("PAH"); Group 2, pulmonary venous hypertension, *i.e.*, pulmonary hypertension related to left-heart disease;

Group 3, pulmonary hypertension associated with disorders damaging the lungs; Group 4, pulmonary hypertension caused by chronic thrombotic or embolic disease, including chronic blood clots in the lungs; and Group 5, a miscellaneous category for conditions that do not fit well into the other four subgroups. Groups 1, 3, 4, and 5 are caused by conditions affecting the pulmonary arteries or precapillary vessels of the lungs ("precapillary PH"), while Group 2 typically develops as a result of a cardiac-based etiology ("postcapillary PH"). Due to differing etiologies, each group may require group-specific treatment.

United Therapeutics owns the '793 and '066 patents, which are generally directed to methods of treating pulmonary hypertension and to pharmaceutical compositions comprising treprostinil. The '793 and '066 patents are listed in the FDA's Orange Book for Tyvaso.

Liquidia filed NDA No. 213005 for Yutrepia™ under § 505(b)(2) of the Food, Drug, and Cosmetic Act (codified at 21 U.S.C. § 355(b)(2)). [1] Yutrepia is a dry powder

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[1] Under the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman amendments to the Food, Drug, and Cosmetic Act), an NDA filed under § 505(b)(2) contains full reports of investigations of safety and effectiveness, where at least some of the information used for approval comes from studies that were not conducted for or by the applicant. Such an NDA is one of two abbreviated approval pathways introduced by the Hatch-Waxman amendments, the other being an abbreviated new drug application ("ANDA") filed under § 505(j) (codified at 21 U.S.C. § 355(j)). 35 U.S.C. § 271(e)(2), the statutory provision delineating acts of infringement, covers both types of applications: "It shall be an act of infringement to submit . . . an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in

inhalation formulation of treprostinil but is not a generic version of any currently marketed drug. Pursuant to § 505(c)(3)(C) (codified at 21 U.S.C. § 355(c)(3)(C)), United Therapeutics sued Liquidia within 45 days of receipt of notice of Liquidia's NDA in the United States District Court for the District of Delaware alleging infringement of the '066 patent. J.A. 171, 190. In addition, after Liquidia filed its NDA, United Therapeutics filed another patent application that eventually issued as the '793 patent, which was subsequently added to the district court litigation. J.A. 208.

In parallel, Liquidia filed a petition for *inter partes* review ("IPR") of the '793 patent, alleging that all claims would have been unpatentable as obvious over prior art at the time of the invention. On July 19, 2022, the Board issued a Final Written Decision finding all claims of the '793 patent unpatentable as obvious. *Liquidia Techs., Inc. v. United Therapeutics Corp.*, No. IPR2021-00406, 2022 WL 2820717 (P.T.A.B. July 19, 2022). United Therapeutics filed a Request for Rehearing, challenging whether various asserted references qualified as prior art. J.A. 36648. In its Rehearing Decision, the Board found that the references were prior art, again holding the claims of the '793 patent unpatentable as obvious. United Therapeutics filed a Notice of Appeal in that case on April 26, 2023. Liquidia filed a motion for expedited appeal, which has been denied. The appeal is currently pending in this court.

I. The '793 Patent

The '793 patent is directed to a method of treating pulmonary hypertension comprising inhalation of treprostinil. Asserted claim 1 of the '793 patent is the only independent claim and reads as follows:

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section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent[.]"

> 1. A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.

'793 patent at col. 18 ll. 23–31.

The additional asserted dependent claims include limitations directed to dry powder inhalers (claim 4), powder formulations (claim 6), powder formulations comprising particles less than 5 micrometers in diameter (claim 7), and formulations containing no metacresol (claim 8). *See id.* col. 18 ll. 36–37, 40–45.

In the district court, United Therapeutics argued that, although Liquidia's proposed product had not yet been marketed, when marketed, it (1) would directly infringe claims 1, 4, and 6–8 of the '793 patent and (2) would also induce infringement of those claims. Liquidia responded that the asserted claims were invalid as lacking adequate enablement and written description under 35 U.S.C. § 112.

The district court found that United Therapeutics showed that a single administration of treprostinil, as required by claim 1, improves a patient's hemodynamics, establishing that administration of Liquidia's Yutrepia, comprising treprostinil, at the claimed doses will also improve a patient's hemodynamics. The court concluded that United Therapeutics thus proved by a preponderance of the evidence that the administration of Yutrepia will directly infringe claims 1, 4, and 6–8 of the '793 patent.

The district court also concluded that Liquidia's argument that it lacked specific intent to induce infringement lacked merit. Liquidia argued that, because the Yutrepia label does not encourage administration of a therapeutically effective single event dose, it does not induce infringement. The court noted that the label does not need to provide hemodynamic data to constitute inducement of infringement; instead, it merely needs to instruct doctors and patients to administer a therapeutically effective single event dose. The court found that the label's instructions will inevitably lead to the administration of a therapeutically effective single event dose. The court thus concluded that United Therapeutics proved by a preponderance of the evidence that Liquidia will induce infringement of claims 1, 4, and 6–8 of the '793 patent.

The district court further found that the asserted claims were not invalid for lack of enablement or written description. First, the court construed "treating pulmonary hypertension" as encompassing all five groups of pulmonary hypertension, noting that the specification of the '793 patent expressly includes all five groups when describing "pulmonary hypertension." Second, the court found that a skilled artisan would not need to engage in undue experimentation to practice the full scope of the claimed treatment of pulmonary hypertension, despite potential safety concerns in treating Group 2 PH patients, and that the claims did not require safety and efficacy. Third, the court found that the claims were not invalid for lack of written description, finding that a skilled artisan would, based on the specification, understand that treprostinil would effectively vasodilate the pulmonary vasculature, improve hemodynamics, and treat a patient's elevated pulmonary blood pressure. As a result of the court's findings that the claims were not invalid but were infringed, the court stayed approval of Liquidia's NDA for Yutrepia until May 5, 2027, the expiration date of the '793 patent.

II. The '066 Patent

The '066 patent is directed to a pharmaceutical composition comprising treprostinil and a process of preparing a pharmaceutical product comprising treprostinil.

Asserted claim 1 of the '066 patent reads as follows:

> 1. A pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof, said composition prepared by a process comprising providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps, forming a salt of treprostinil by combining the starting batch and a base, isolating the treprostinil salt, and preparing a pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of the treprostinil is lower in the pharmaceutical composition, and wherein said alkylation is alkylation of benzindene triol.

'066 patent at col. 17 ll. 51–63.

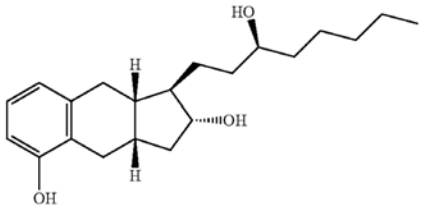
Asserted claim 6 of the '066 patent reads:

> 6. The pharmaceutical composition of claim 1, wherein the isolated salt is stored at ambient temperature.

Id. col. 18 ll. 34–35.

Asserted claim 8 of the '066 patent reads:

> 8. A process of preparing a pharmaceutical product comprising treprostinil or a pharmaceutically acceptable salt thereof, comprising alkylating a triol intermediate of the formula:



> hydrolyzing the resulting compound to form treprostinil, forming a salt of treprostinil stable at ambient temperature, storing the treprostinil salt at ambient temperature, and preparing a pharmaceutical product from the treprostinil salt after storage, wherein the pharmaceutical product comprises treprostinil or a pharmaceutically acceptable salt thereof.

Id. col. 18 ll. 38–61.

Additional asserted dependent claims are directed to crystalline forms (claim 2), a base selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline (claim 3), and a pharmaceutical product prepared by the process recited in claim 8 (claim 9). *See id.* col. 17 ll. 64–67; col. 18 ll. 27–28, 62–63.

In the district court, United Therapeutics argued that Liquidia infringed claims 1–3, 6, 8, and 9 of the '066 patent. Liquidia responded that claims 1–3, 6, and 9 were invalid as anticipated by Moriarty[2] and that claims 1–3 and 6 were invalid as lacking written description support. Liquidia did not challenge the validity of claim 8, which is a chemical

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[2] R.M. Moriarty et al., *The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)*, 69 J. ORGANIC CHEM. 1890 (2004).

process claim, in contrast to the other claims that are directed to compositions.

The district court found that United Therapeutics showed by a preponderance of the evidence that Liquidia's Yutrepia would infringe claims 1–3 of the '066 patent because Yutrepia met the impurities limitations of claim 1. But the court also found that claims 1–3, 6, and 9 were invalid as anticipated by Moriarty. Moriarty discloses the synthesis of analogues of benzindene prostacyclins, including treprostinil, which is designated in the publication as UT-15. Moriarty at 1890, 1892. The court also found that Liquidia showed by clear and convincing evidence that the claimed treprostinil product is functionally and structurally the same as the UT-15 treprostinil disclosed in Moriarty. The court thus concluded that claims 1–3 would have been infringed by Liquidia, but for the finding of anticipation, and that claims 6 and 9 were invalid as anticipated by Moriarty but not infringed by Liquidia.

In finding a lack of infringement of claim 6, the court construed the terms "ambient temperature" as room temperature (equal to or less than the range of 15°C to 30°C) and "stored"/"storing"/"storage" to have its plain and ordinary meaning. Using these constructions, the court determined that United Therapeutics failed to show by a preponderance of the evidence that Liquidia's Yutrepia production process stored treprostinil at ambient temperature, and therefore found that claims 6, 8, and 9 were not infringed. The court further found that any storage between steps of Liquidia's manufacturing process did not meet the limitations of claims 8 and 9, which require storage of treprostinil before preparing a pharmaceutical product.

The district court also found that the specification provided adequate written description support for the impurities limitation in claim 1, and that a skilled artisan would understand that the inventors were in possession of the

composition with the claimed impurities. The court thus concluded that Liquidia did not prove by clear and convincing evidence that claims 1–3 and 6 of the '066 patent were invalid for lack of written description.

In summary, the district court concluded that (1) claims 1, 4, and 6–8 of the '793 patent were not invalid and were infringed by Liquidia; (2) claims 1–3 of the '066 patent were invalid as anticipated by Moriarty and would have been infringed by Liquidia but for the finding of anticipation; (3) claims 6 and 9 of the '066 patent were invalid as anticipated by Moriarty and not infringed by Liquidia; and (4) claim 8 of the '066 patent was not invalid and not infringed by Liquidia. Liquidia appealed, and United Therapeutics cross-appealed. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

Liquidia raises five issues on appeal. First, Liquidia contends that the district court erred in construing the claim limitation "treating pulmonary hypertension" in claim 1 of the '793 patent not to include safety and efficacy. Second, Liquidia argues that the court erred in finding the asserted claims of the '793 patent enabled. Third, Liquidia contends that the court clearly erred in finding the asserted claims of the '793 patent supported by written description. Fourth, Liquidia contends that the court clearly erred in finding Liquidia liable for induced infringement of claims 1, 4, and 6–8 of the '793 patent. Fifth, Liquidia argues that the court clearly erred in finding claims 1–3 of the '066 patent to be infringed.

United Therapeutics raises two issues on cross-appeal. First, United Therapeutics asserts that the district court clearly erred in finding that Liquidia does not infringe claims 6 and 8 of the '066 patent. Second, United Therapeutics contends that the court clearly erred in finding that claims 1–3, 6, and 9 of the '066 patent are invalid as

anticipated by Moriarty. We address each appeal and cross-appeal argument in turn.

Infringement is a question of fact that we review, after a bench trial, for clear error. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1364 (Fed. Cir. 2017). A patent is directly infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent." 35 U.S.C. § 271(a). "Whoever actively induces infringement of a patent shall be liable as an infringer." *Id.* § 271(b).

We review district court findings of anticipation under 35 U.S.C. § 102 and satisfaction of the written description requirement under 35 U.S.C. § 112 for clear error. *Nuvo Pharms. (Ir.) Designated Activity Co. v. Dr. Reddy's Lab'ys Inc.*, 923 F.3d 1368, 1376 (Fed. Cir. 2019) (written description); *Forest Lab'ys, Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268 (Fed. Cir. 2007) (anticipation). Enablement "is a question of law" that we review *de novo* after a bench trial. *Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1281 (Fed. Cir. 2007). We review questions of claim construction *de novo* but review any underlying facts for clear error. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979, 991 (Fed. Cir. 1995); *Eli Lilly & Co. v. Hospira, Inc.*, 933 F.3d 1320, 1328 (Fed. Cir. 2019).

I. The '793 Patent

A.

We first consider Liquidia's challenge to the district court's determination that the meaning of "treating pulmonary hypertension" does not require a showing of safety and efficacy. It asserts that a skilled artisan would understand the plain and ordinary meaning of "treating pulmonary hypertension" to encompass a method that accomplishes that goal safely and effectively. It asserts

that the parties' experts agreed that treatment with treprostinil, a vascular dilator, would not benefit Group 2 PH patients. It further asserts that while the specification of the '793 patent states that the treatment does not result in significant side effects, '793 patent at col. 5 ll. 16–20, and that administration of treprostinil is safe, *id.* col. 9 ll. 30–31, its expert testified that a skilled artisan would have concerns about administering inhaled treprostinil to Group 2 PH patients and that at least one earlier study, in which a treprostinil-like prostacyclin was administered to Group 2 PH patients, failed due to increased mortality.

United Therapeutics responds that the district court did not err in finding that the claimed administration of treprostinil would improve hemodynamics and hence treat a patient's elevated pulmonary blood pressure, including Group 2 PH patients. It asserts that Liquidia attempts to import limitations into the claims and that nothing in the specification requires the importation of safety and efficacy limitations into the claims. Finally, United Therapeutics asserts that while Liquidia's statements that a skilled artisan would have safety concerns in treating Group 2 PH patients with treprostinil may factor into Food and Drug Administration ("FDA") approval, they do not factor into claim interpretation.

As a threshold matter, we agree with the district court that "treating pulmonary hypertension" includes treating all five groups of pulmonary hypertension patients. The court did not err in finding that the specification encompasses all five groups when describing "pulmonary hypertension." In fact, the specification does not limit the scope of "pulmonary hypertension" to any particular subset of pulmonary hypertension patients. It refers to both "precapillary pulmonary hypertension" and "pulmonary hypertension," which, as the court found, demonstrates that the inventors view precapillary PH only as a subset of the broadly claimed "pulmonary hypertension." Thus, "treating pulmonary hypertension" includes treating all five

groups of pulmonary hypertension. *See* '793 patent at col. 9 ll. 36–37, col. 12 ll. 64–65, col. 16 ll. 64–65.

While the claims require "treating pulmonary hypertension comprising administering . . . a therapeutically effective single event dose of a formulation comprising treprostinil," *Decision*, at 467, the district court gave the phrase "therapeutically effective" a limiting construction. The district court held, and Liquidia does not challenge on appeal, that a person of ordinary skill in the art "would understand the plain and ordinary meaning of 'therapeutically effective single dose' to be a dose given in a single treatment session that causes an improvement in a patient's hemodynamics (reduced PAP or PVR)." *Id.* at 461; Appellee's Br. 39. We need not address whether the district court's construction was correct because Liquidia, on appeal, does not challenge that construction. Read in context, the claim language "treating pulmonary hypertension" does not import any additional efficacy limitations or any safety limitations.

Absent incorporation of safety and efficacy requirements in the claims, Liquidia's argument concerning the safety and efficacy of treating Group 2 PH patients is not before us. Questions of safety and efficacy in patent law have long fallen under the purview of the FDA. *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995) (noting that "the requirements under the law for obtaining a patent" are different from "the requirements for obtaining government approval to market a particular drug for human consumption"); *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness . . . is more properly left to the [FDA]. Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings."); *In re Anthony*, 414 F.2d 1383, 1395 (CCPA 1969) ("Congress has given the responsibility to the FDA, not to the Patent Office, to determine in the first instance whether drugs are sufficiently safe for use that they can be introduced in the commercial

market . . . ."). We decline to insert the FDA's responsibilities into claims by importing requirements where they do not recite such limitations.

B.

We next turn to Liquidia's challenge to the district court's finding that the claims of the '793 patent are adequately enabled and supported by written description. Liquidia argues that the specification of the '793 patent provides no guidance or examples of treating Group 2 PH patients, and thus that a skilled artisan would have to engage in undue experimentation to practice the full scope of the claimed invention (*i.e.*, treating Group 2 PH patients).

Liquidia further argues that, even if the district court's construction of "treating pulmonary hypertension" as not requiring safety was proper, the claims of the '793 patent would still not be enabled because any changes in hemodynamics caused by inhalation of treprostinil would provide no benefit to Group 2 PH patients. Thus, a skilled artisan would not conclude that the '793 patent claims are enabled to the full scope of the claimed invention.

United Therapeutics responds that the district court did not err in concluding that Liquidia failed to show a lack of enablement. It contends that Liquidia failed to show by clear and convincing evidence that enablement would require undue experimentation with respect to Group 2 PH.

Further, even if the specification fails to describe how to treat Group 2 PH patients with treprostinil, United Therapeutics asserts, claims are not required to carve out all possible inoperative embodiments in a claim in order to avoid that claim being found not to be enabled. United Therapeutics asserts that if a skilled artisan has the information to limit the claims to operative embodiments, then the claims are not invalid. Here, United Therapeutics asserts, the skilled artisan has that information.

Liquidia also challenges the district court's finding that the claims are supported by an adequate written description. Liquidia argues that the '793 patent never describes treating Group 2 PH patients with inhaled treprostinil, but only Group 1, 3, and 4 patients, all of whom have precapillary PH. Thus, Liquidia contends, there is no information in the '793 patent specification sufficient for a skilled artisan to conclude that the inventors were in possession of a method of treating Group 2 PH patients with inhaled treprostinil.

Liquidia further argues that, even if the district court correctly construed "treating pulmonary hypertension" not to require a showing of safety, the claims still are not supported by written description because vasodilation of the pulmonary vasculature is not effective in treating Group 2 PH patients. Thus, Liquidia contends, a skilled artisan would have understood that the inventors did not invent or possess a method of treating Group 2 PH patients.

United Therapeutics responds that the district court did not clearly err in finding the claims of the '793 patent supported by an adequate written description. United Therapeutics argues that Liquidia's written description arguments fail for largely the same reasons as its enablement arguments. In particular, United Therapeutics asserts that the court did not err in holding that a skilled artisan would understand a therapeutically effective dose to be one that improves a patient's hemodynamics. United Therapeutics further contends that, although a physician may or may not decide to administer treprostinil to a Group 2 PH patient, that decision would be informed by FDA guidance, not the written description in the specification.

We agree with United Therapeutics that the claims are adequately enabled as they were construed by the district court. The specification of the '793 patent sufficiently enables the scope of the claims. *See, e.g.*, '793 patent at col. 7 ll. 7–67 (providing details on administration,

concentrations, and dosages of inhaled treprostinil for treating patients with pulmonary hypertension); *id.* col. 9 ll. 5–49 (describing an open label study upon acute safety, tolerability, and hemodynamic effects of inhaled treprostinil delivered over the course of a few seconds). While the court credited expert testimony concluding that a physician may have safety concerns in treating Group 2 PH patients with treprostinil and other vasodilators, *see Decision*, at 466–67, the court also found that the record demonstrates that the claimed administration of treprostinil vasodilates the pulmonary vasculature and reduces pulmonary blood pressure even in Group 2 PH patients, *id.* at 468. The court properly relied on expert testimony and record evidence to conclude that a skilled artisan would understand that the claimed administration of treprostinil would vasodilate the pulmonary vasculature, improve hemodynamics, and in this way for a single dose, treat a patient's elevated pulmonary blood pressure independent of the type (*i.e.*, group) of pulmonary hypertension patient. *Id.* That was all that the claims require under the district court's construction because, again, the parties do not dispute that a "therapeutically effective single event dose" is defined by "an improvement in a patient's hemodynamics (reduced PAP or PVP)." That a study—administering treprostinil-like prostacyclins to Group 2 PH patients—failed due to increased mortality, yet showed "improvement in a patient's hemodynamics," may be an issue for the FDA. But our focus is on the claimed invention. And on this record, with the district court's claim construction, the claims are adequately enabled.

We also agree with United Therapeutics that the district court did not clearly err in finding that the claims of the '793 patent are supported by an adequate written description. Written description requires that the specification reasonably convey to those skilled in the art that the inventor had possession of the claimed invention as of the filing date. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d

1336, 1351 (Fed. Cir. 2010) (en banc). As the court noted, the '793 patent claims require "treating pulmonary hypertension comprising administering . . . a therapeutically effective single event dose of a formulation containing treprostinil," *Decision*, at 466–67, and the specification describes that. In other words, the specification shows possession for the claimed invention under the district court's construction.

Liquidia essentially asks us to treat Group 2 PH as a claimed species within a larger genus (*i.e.*, all five groups of pulmonary hypertension). But analogizing a subset of patients having a variant of a particular disease to traditional genus and species claims is inapt. It would be incorrect to fractionate a disease or condition that a method of treatment claim is directed to, and to require a separate disclosure in the specification for each individual variant of the condition (here, an individual group of pulmonary hypertension patients) in order to satisfy the enablement and written description provisions of 35 U.S.C. § 112, unless these variants are specified in the claims.

Again, because safety and efficacy are not recited in the claims, we need not deal with Liquidia's arguments. Disease-specific treatment requirements are matters for the FDA and medical practitioners. They are best suited to make these determinations because practitioners are informed by the findings of the regulatory agency to avoid treatment of patients who will not properly respond. And every claim to a method of treatment of an ailment has refinements. That is, for any given method of treatment claim, there may be a subset of patients who would not benefit from or should not take the claimed treatment. *See* Oral Arg. at 4:28–4:58, https://oralarguments.cafc.uscourts.gov/default.aspx?fl=22-2217_05032023.mp3. That does not mean that such claims are not sufficiently enabled or supported by written description. A subset of unresponsive patients is not analogous to

unsupported species in a generic claim to chemical compounds.

C.

We next turn to Liquidia's challenge to the district court's finding that Liquidia was liable for induced infringement. Liquidia argues that it cannot be held liable for induced infringement because the '793 patent was found to be unpatentable in an IPR, and an unpatentable or invalid patent cannot be infringed. To support this assertion, Liquidia cites *Commil USA, LLC v. Cisco Systems, Inc.*, 575 U.S. 632, 644 (2015) (stating that if "an act that would have been . . . an inducement to infringe pertains to a patent that is shown to be invalid, there is no patent to be infringed"). Liquidia contends that *Commil* should be read as stating that knowledge of actual unpatentability determined in an IPR precludes having the necessary intent to induce infringement.

United Therapeutics responds that the Board's decision on the '793 patent is not final, and a non-final Board decision does not defeat Liquidia's liability for inducing infringement of the '793 patent. United Therapeutics contends that unpatentability is relevant to infringement liability only once a final adjudication of unpatentability or invalidity rules that there is no such patent to infringe.

We agree with United Therapeutics that the district court did not clearly err in finding that Liquidia induced infringement of the '793 patent. The court did not clearly err in finding that the label on Yutrepia, Liquidia's product, does not need to provide hemodynamic data to constitute inducement of infringement; it merely needs to instruct doctors and patients to administer a therapeutically effective single event dose, which it does. *Decision*, at 462–63. The court also did not clearly err in concluding that United Therapeutics proved that a single administration of Yutrepia will be therapeutically effective, as required by the claims of the '793 patent and constituting inducement.

Liquidia's reliance on *Commil*, 575 U.S. at 632, requires the '793 patent to have been invalidated, but as United Therapeutics argues, the corresponding IPR proceeding of the '793 patent is pending on appeal in this court. A pending, non-final litigation does not negate an intent to infringe that is otherwise supported by evidence. And we have previously held that an IPR decision does not have collateral estoppel effect until that decision is affirmed or the parties waive their appeal rights. *XY, LLC v. Trans Ova Genetics, L.C.*, 890 F.3d 1282, 1294 (Fed. Cir. 2018) ("[A]n affirmance of an invalidity finding, whether from a district court or the Board, has a collateral estoppel effect on all pending or co-pending actions."). Further, as the court noted, the Board's final written decision does not cancel claims; the claims are cancelled when the Director issues a certificate confirming unpatentability, which occurs only after "the time for appeal has expired or any appeal has terminated." 35 U.S.C. § 318(b). The '793 IPR decision thus has no impact here on a finding of induced infringement.

II. The '066 Patent

A.

We next turn to Liquidia's assertion on appeal that the district court clearly erred in finding that it infringed claims 1–3 of the '066 patent. Liquidia argues that United Therapeutics failed to meet its burden of proving infringement. In particular, Liquidia argues that United Therapeutics identified the starting batch as the treprostinil salt and the pharmaceutical composition as the bulk powder. Liquidia thus contends that a comparison between the impurities in the treprostinil salt and bulk powder would have been required to establish infringement of claims that require a lowering of impurities.

United Therapeutics responds that the district court did not clearly err in finding that Liquidia infringed claims 1–3 of the '066 patent. United Therapeutics contends that

the court based its conclusion on well-supported facts in finding that a skilled artisan would understand the relevant impurities to be those generated during the alkylation and hydrolysis steps used to create the starting batch of treprostinil.

We need not evaluate this argument that claims 1–3 of the '066 patent are not infringed, because Liquidia correctly argues that the district court did not clearly err in finding those claims invalid as anticipated by Moriarty. *See* Part II.B. Because unpatentable or invalid claims cannot be infringed, *Commil*, 575 U.S. at 644 ("To say that an invalid patent cannot be infringed . . . is in one sense a simple truth, both as a matter of logic and semantics."), the issue of infringement of claims 1–3 of the '066 patent has been rendered moot.

B.

Accordingly, we forthwith turn to United Therapeutics' argument on cross-appeal concerning the validity of claims 1–3. United Therapeutics argues that Moriarty does not teach the purification of treprostinil through salt formation and discloses no information on specific alkylation and hydrolysis impurities. United Therapeutics argues that it added the relevant impurities claim language to overcome validity challenges raised during prosecution, and the court failed to recognize the structural features that are imparted by the claimed salt-formation purification. United Therapeutics further contends that Moriarty discloses treprostinil with a purity of 99.7%, which does not establish that the product of Moriarty had the same level of alkylation or hydrolysis impurities of the claimed product.

Liquidia responds that the district court did not err in finding that claims 1–3, 6, and 9 of the '066 patent are anticipated by Moriarty. Liquidia argues that the claimed composition in Moriarty is the same as the claimed

composition in the '066 patent, and that United Therapeutics demonstrated no clear error in the court's findings.

We agree with Liquidia that the district court did not clearly err in finding that claims 1–3, 6, and 9 are invalid as anticipated by Moriarty. The claims of the '066 patent are directed to a pharmaceutical composition comprising, *inter alia*, treprostinil, prepared by alkylation and hydrolysis steps. It is thus referred to as a product-by-process claim. But a product-by-process claim is a product claim, even if claimed by a process by which it can be made. The claims also recite the presence of impurities.

We conclude that the district court did not clearly err in finding that these claims are anticipated by the Moriarty reference, which discloses treprostinil with impurities. The specification of the '066 patent discloses an impurity level of 99.7%–99.9%, '066 patent col. 14, table, whereas Moriarty similarly discloses the synthesis of impure treprostinil, designated in the publication as UT-15, having 99.7% purity, Moriarty at 1890, 1892, 1902. As these claims are product claims, they are anticipated by a disclosure of the same product irrespective of the processes by which they are made. Further, United Therapeutics did not provide any expert or fact witness rebutting Liquidia's expert's opinions or providing testimony identifying any structural or functional differences between the Moriarty treprostinil and the claimed treprostinil. *Decision*, at 456. The court thus did not err in finding that claims 1–3, 6, and 9 of the '066 patent are anticipated by Moriarty.

C.

United Therapeutics also argues on cross-appeal that the district court clearly erred in finding that Liquidia does not infringe claims 6 and 8 of the '066 patent. United Therapeutics contends that claims 6 and 8 require that the treprostinil salt be stored at ambient temperature, and that Liquidia stores treprostinil salt at ambient temperature during production, thus infringing the claims. United

Therapeutics contends that Liquidia's promise not to make its product with batches of treprostinil salt that were stored at ambient temperature is insufficient to avoid a finding of infringement.

United Therapeutics also contends that the district court erred in construing the term "storage" in claims 6 and 8 as excluding storage during manufacturing but including storage during shipment of the product. United Therapeutics further contends that Liquidia also infringes claim 8 through ambient storage that occurs after the composition recited in claims 1–6 is prepared and before the drug product of claim 8 is prepared.

Liquidia responds that the district court did not clearly err in finding that it does not infringe claims 6 and 8 of the '066 patent. In particular, Liquidia notes that the court based its findings of non-infringement on several clear findings of fact, including that (1) Liquidia's NDA requires the treprostinil salt to be stored at a temperature of 2–8°C; (2) Liquidia asserted that it would not use treprostinil salt batches that have been stored at ambient temperature; and (3) Liquidia begins preparing a pharmaceutical product during step 1 of its production process. Liquidia further asserts that the NDA storage specifications are regulatory requirements, not mere recommendations or promises.

Liquidia further responds that the district court did not err in its construction of the term "storage." Liquidia asserts that United Therapeutics mischaracterizes Liquidia's production process, and that its production process is a single production process, not two stages separated by a period of ambient storage.

We agree with Liquidia that the district court did not clearly err in finding that it does not infringe claims 6 and 8 of the '066 patent. The court credited Liquidia's representations to the FDA that it would store treprostinil sodium between 2°C and 8°C. The court also found that United Therapeutics provided no evidence showing that

Liquidia used ambient-temperature-stored batches of treprostinil in its manufacturing process in making a pharmaceutical composition as required by claim 6 or claim 8. Without a showing that Liquidia stores treprostinil at ambient temperature, there can be no infringement of the claims.

CONCLUSION

We have considered the parties' remaining arguments but find them unpersuasive. For the foregoing reasons, the decision of the United States District Court for the District of Delaware is affirmed.

AFFIRMED

COSTS

No costs.

CERTIFICATE OF SERVICE

I hereby certify that on August 23, 2023, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit using the Court's CM/ECF system. Counsel for all parties to the case are registered CM/ECF users and will be served by the CM/ECF system.

CERTIFICATE OF COMPLIANCE

I certify that this brief complies with the type-volume limitation of Fed. R. App. P. 35(b)(2)(A) because it contains 3,513 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(f) and Fed. Cir. R. 32(b)(2).

I further certify that this petition complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type-style requirements of Fed. R. App. P. 32(a)(6) because it has been prepared using Microsoft Word for Office 365 in 14-point Century Schoolbook, a proportionally spaced font.

August 23, 2023 /s/ *Jaime A. Santos*
Jaime A. Santos